PATENT

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Original). A water-soluble polymer having the structure:

POLY
$$X' = \begin{bmatrix} R^1 \\ I \\ C \\ R^2 \end{bmatrix}_{z'} C - H$$

I

wherein:

POLY is a water-soluble polymer segment;

X' is a linker moiety;

z' is an integer from 1 to about 21;

R¹, in each occurrence, is independently H or an organic radical selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkynyl, aryl, and substituted aryl;

R², in each occurrence, is independently H or an organic radical selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkynyl, aryl, and substituted aryl,

and further wherein the following apply:

-when POLY is linear:

- (a) the total number of carbonyls present in said polymer is 0 or 2 or greater except when X' comprises one or more contiguous (-CH₂CH₂O-) segments,
- (b) and further wherein X' is oxygen or comprises at least one (-CH₂CH₂O-) segment and z' is from 2 to 12, then at least one of R¹ or R² in at least one occurrence is an organic radical as defined above or said polymer is heterobifunctional, where POLY comprises a reactive group at one terminus that is not hydroxy, and

PATENT

-when POLY is branched:

(c) either (i) at least one of R^1 or R^2 in at least one occurrence is an organic radical as defined above or (ii) X' includes -(CH_2CH_2O)_b- where b is from 1 to about 20 in the instance where POLY comprises a lysine residue,

(d) and further wherein said POLY has 2 polymer arms, then neither polymer arm comprises oxygen as the only heteroatom in the instance where POLY comprises "C-H" as a branch point.

- 2. (Original). The polymer of claim 1, wherein z' ranges from 2 to 21.
- 3. (Original). The polymer of claim 1, wherein z' ranges from 3 to 12.
- 4. (Original). The polymer of claim 1, having the structure:

POLY—X'—
$$C_4$$
— C_3 — C_2 — C_1 —H
 R^2 R^2 R^2

wherein POLY, X', each R¹, each R² and R³ are as previously defined.

- 5. (Original). The polymer of claim 4, wherein the R^1 attached to C_2 is alkyl, and all other R^1 and R^2 variables are H.
 - 6. (Original). The polymer of claim 5, wherein the R^1 attached to C_2 is lower alkyl.
- 7. (Original). The polymer of claim 6, wherein the R^1 attached to C_2 is selected from the group consisting of methyl, ethyl and propyl.

8. (Original). The polymer of claim 4, wherein the R¹ attached to C₃ is alkyl, and all other R¹ and R² variables are H.

- 9. (Original). The polymer of claim 8, wherein the R¹ attached to C₃ is lower alkyl.
- 10. (Original). The polymer of claim 4, wherein the R¹ attached to C₄ is alkyl, and all other R¹ and R² variables are H.
 - 11. (Original). The polymer of claim 10, wherein the R^1 attached to C_4 is lower alkyl.
 - 12. (Original). The polymer of claim 1, having the structure:

POLY—X—
$$C_5$$
— C_4 — C_3 — C_2 — C_1 — C_1 — C_4

wherein POLY, X', and each R¹ and each R² are as previously defined.

- 13. (Original). The polymer of claim 12, wherein the R¹ attached to C₂ is alkyl, and all other R¹ and R² variables are H.
- 14. (Original). The polymer of claim 12, wherein either the R¹ attached to C₃ or C₄ is alkyl, and all other R¹ and R² variables are H.
 - 15. (Original). The polymer of claim 1, having the structure:

POLY — X:—
$$C_6$$
 — C_5 — C_4 — C_3 — C_2 — C_1 — C_4 — C

Atty Dkt No. 6800-0073

USSN: 10/659,734 PATENT

wherein POLY, X', and each R¹ and each R² are as previously defined.

- 16. (Original). The polymer of claim 15, wherein the R^1 attached to C_2 is alkyl, and all other R^1 and R^2 variables are H.
- 17. (Currently Amended). The polymer of claim 15, wherein one of the R^1 variables attached to C_3 or C_4 or C_5 is alkyl, and all other R1 and R2 R^1 and R^2 variables are H.
- 18. (Original). The polymer of claim 1, wherein X' comprises a moiety corresponding to the structure:

$$-(CH_2)_c-D_e-(CH_2)_f$$
 or $-(CH_2)_p-M_r-C(O)-K_s-(CH_2)_q$

wherein:

c is zero to 8,

D is O, NH, or S,

e is 0, 1

f is zero to 8,

p is zero to 8,

M is –NH, O

K is NH, O

q is from zero to 8, and

r and s are each independently 0, 1.

- 19. (Original). The polymer of claim 1, wherein X' includes a moiety corresponding to the structure -(CH₂CH₂O)_b- or -(CH₂CH₂NH)_g-, and b and g are each independently 1 to 20.
 - 20. (Original). The polymer of claim 19, wherein b and g are each independently 1 to 10.
 - 21. (Original). The polymer of claim 20, wherein b and g are each independently 1 to 6.

PATENT

22. (Original). The polymer of claim 18, wherein X' comprises a moiety corresponding to the structure:

$$-(CH_2)_c-D_e-(CH_2)_f-P-$$
 or $-(CH_2)_p-M_r-C(O)-K_s-(CH_2)_q-T-$

wherein:

P and T are each independently -(CH₂CH₂O)_b- or -(CH₂CH₂NH)_g, b and g are each independently 1 to 20, and the remaining variables are as defined in claim 18.

- 23. (Original). The polymer of claim 1, wherein said X' comprises –C(O)NH-(CH₂)₁. ₆NH-C(O)- or –NHC(O)NH-(CH₂)₁₋₆NH-C(O)-.
- 24. (Original). The polymer of claim 1, wherein POLY is selected from the group consisting of poly(alkylene oxide), poly(vinyl pyrrolidone), poly(vinyl alcohol), polyoxazoline, poly(acryloylmorpholine), and poly(oxyethylated polyol).
 - 25. (Original). The polymer of claim 1, wherein POLY is a poly(alkylene oxide).
 - 26. (Original). The polymer of claim 25, wherein POLY is a poly(ethylene glycol).
- 27. (Original). The polymer of claim 26, wherein the poly(ethylene glycol) is terminally capped with an end-capping moiety.
- 28. (Original). The polymer of claim 27, wherein the end-capping moiety is independently selected from the group consisting alkoxy, substituted alkoxy, alkenyloxy, substituted alkenyloxy, alkynyloxy, substituted alkynyloxy, substituted aryloxy.
- 29. (Original). The polymer of claim 28, wherein the end-capping moiety is selected from the group consisting of methoxy, ethoxy, and benzyloxy.

PATENT

30. (Original). The polymer of claim 26, wherein the poly(ethylene glycol) has a nominal average molecular mass of from about 100 daltons to about 100,000 daltons.

- 31. (Original). The polymer of claim 26, wherein the poly(ethylene glycol) has a nominal average molecular mass of from about 1,000 daltons to about 50,000 daltons.
- 32. (Original). The polymer of claim 26, wherein the poly(ethylene glycol) has a nominal average molecular mass of from about 2,000 daltons to about 30,000 daltons.
 - 33. (Original). The polymer of claim 1, comprising the structure:

$$H = \begin{bmatrix} C & \begin{bmatrix} R^1 \\ I \\ C \end{bmatrix} \\ R^2 \end{bmatrix}_{z'} X' = POLY = \begin{bmatrix} C & C \\ I \\ R^2 \end{bmatrix}_{z'} C = H$$

II

wherein POLY, each X', each (z'), and each R¹ and each R² are as previously defined.

- 34. (Original). The polymer of claim 33, wherein said POLY is linear and the polymer is homobifunctional.
- 35. (Original). The polymer of claim 26, wherein said poly(ethylene glycol) has a structure selected from the group consisting of linear, branched and forked.
- 36. (Original). The polymer of claim 26, wherein said poly(ethylene glycol) comprises the structure:

$$Z-(CH_2CH_2O)_n$$
- or $Z-(CH_2CH_2O)_n$ - CH_2CH_2 -,

where n is from about 10 to about 4000, and Z comprises a moiety selected from the

PATENT

group consisting of hydroxy, amino, ester, carbonate, aldehyde, alkenyl, acrylate, methacrylate, acrylamide, sulfone, thiol, carboxylic acid, isocyanate, isothiocyanate, hydrazide, maleimide, vinylsulfone, dithiopyridine, vinylpyridine, iodoacetamide, alkoxy, benzyloxy, silane, lipid, phospholipid, biotin, and fluorescein.

37. (Original). The polymer of claim 1, having a structure selected from the group consisting of:

III-A

$$PEG-(CH_2)_a - \overset{O}{C}-NH-(CH_2CH_2NH)_g - \begin{bmatrix} R^1 \\ C \\ R^2 \end{bmatrix} \overset{O}{C}-H$$

IV-A

III-C

IV-C

wherein PEG is poly(ethylene glycol), b and g are each independently 0 to 20, a is 0 to 6, and the remaining variables are as defined in claim 1.

PATENT

38. (Original). The polymer of claim 37, having the structure:

$$PEG \stackrel{O}{-C-NH} - (CH_2CH_2O)_b \stackrel{\left[\begin{matrix} R^1 \\ I \end{matrix}\right]}{-C-H} \stackrel{O}{-C-H}$$

III-B

or

$$PEG - C-NH - (CH2CH2NH)g - \begin{bmatrix} R^1 \\ C \\ R^2 \end{bmatrix} C - H$$

IV-B

wherein the variables are as defined as in claim 37.

- 39. (Original). The polymer of claim 37, wherein PEG has a structure selected from the group consisting of linear, branched, and forked.
- 40. (Original). The polymer of claim 37, wherein b and g each independently are from 1-8.
- 41. (Original). The polymer of claim 37, wherein b and g each independently are from 1 to 6.
 - 42. (Original). The polymer of claim 37, wherein z' is from 2 to 6.
 - 43. (Original). The polymer of claim 37, wherein z' is 3.
 - 44. (Original). The polymer of claim 37, wherein a is 0 or 1.

PATENT

45. (Original). The polymer of claim 37, having the structure:

III-D

46. (Original). The polymer of claim 45, wherein "PEG" is a poly(ethylene glycol) having a structure corresponding to:

$$Z-(CH_2CH_2O)_n$$
-,

or

$$\begin{array}{c|c} & O & \\ & II & \\ & Z\text{-}(CH_2CH_2O)_n\text{-}C \longrightarrow NH \\ & & (CH_2)_4 \\ & O & | \\ & & \\ Z\text{-}(CH_2CH_2O)_n\text{-}C-NH---CH \longrightarrow \end{array}$$

V

wherein n in each occurrence is independently from about 10 to about 4000, and Z comprises a moiety selected from the group consisting of hydroxy, ester, carbonate, aldehyde, alkenyl, acrylate, methacrylate, acrylamide, sulfone, thiol, carboxylic acid, isocyanate, isothiocyanate, maleimide, vinylsulfone, dithiopyridine, vinylpyridine, iodoacetamide, alkoxy, benzyloxy, silane, phospholipid, biotin, and fluorescein.

47. (Original). The polymer of claim 46, wherein Z is alkoxy, and n in each occurrence is the same and ranges from about 100 -600.

Atty Dkt No. 6800-0073

USSN: 10/659,734 PATENT

48. (Original). The polymer of claim 1, having the structure:

VI-A

or

PEG
$$+ (CH_2)_s - NH-C-NH - (CH_2CH_2O)_b$$
 $\begin{bmatrix} R^1 \\ C \\ R^2 \end{bmatrix}_{z'}^{O}$ d

VI-B

wherein:

PEG is poly(ethylene glycol),

b is 0 to 20,

s is 0 to 6,

d is 1, 2 or 3,

and the remaining variables are as defined in claim 1.

- 49. (Original). The polymer of claim 48, wherein PEG is linear or branched.
- 50. (Original). The polymer of claim 48, wherein R¹ and R² in each occurrence are H.
- 51. (Original). The polymer of claim 48, wherein z' ranges from 3 to 12.
- 52. (Original). The polymer of claim 48, wherein z' is 3.

PATENT

53. (Original). The polymer of claim 48, wherein d is 2 and PEG corresponds to the structure:

$$\begin{array}{c} {\displaystyle \mathop{\rm C}_{\rm II} \atop {\displaystyle \mathop{\rm H}_{\rm CH_2CH_2O}_{\rm in}} - \mathop{\rm C}_{\rm N-CH}} \end{array} \\$$

wherein n is from about 10 to about 4000, Z comprises a moiety selected from the group consisting of hydroxy, ester, carbonate, aldehyde, alkenyl, acrylate, methacrylate, acrylamide, sulfone, thiol, carboxylic acid, isocyanate, isothiocyanate, maleimide, hydrazide, vinylsulfone, dithiopyridine, vinylpyridine, iodoacetamide, alkoxy, benzyloxy, silane, lipid, phospholipid, biotin, and fluorescein, and the remaining variables are as defined in claim 48.

- 54. (Original). The polymer of claim 53, wherein Z is alkoxy or benzyloxy, n ranges from about 200 to about 1500, and b is from 1 to 8.
 - 55 81. (Canceled).
 - 82. (Original). A hydrate or acetal form of the water-soluble polymer of claim 1.
 - 83. (Canceled).
- 84. (Original). The acetal of claim 82, wherein said acetal is selected from the group consisting of dimethyl acetal, diethyl acetal, di-isopropyl acetal, dibenzyl acetal, 2,2,2-trichloroethyl acetal, bis(2-nitrobenzyl) acetal, S,S'-dimethyl acetal, and S,S'-diethyl acetal.
 - 85. (Original). A water soluble polymer of claim 1, protected as a dioxolane.
 - 86 89. (Canceled).

90. (Original). A conjugate formed by reaction of a biologically active agent with the polymer of claim 1.

- 91 93. (Canceled).
- 94. (Original). A hydrogel formed using the water soluble polymer of claim 1.
- 95 154. (Canceled).
- 155. (New). A polymer of claim 37 having the structure:

where a, b, and each R¹ and R² are as defined in claim 1.

- 156. (New). The polymer of claim 155, wherein all R¹ and R² variables are H.
- 157. (New). The polymer of claim 155, wherein the R¹ attached to C₂ is alkyl, and all other R¹ and R² variables are H.
 - 158. (New). The polymer of claim 157, wherein the R^1 attached to C_2 is lower alkyl.
- 159. (New). The polymer of claim 158, wherein the R¹ attached to C₂ is selected from the group consisting of methyl, ethyl and propyl.
- 160. (New). The polymer of claim 155, wherein the R¹ attached to C₃ is alkyl, and all other R¹ and R² variables are H.

Atty Dkt No. 6800-0073

USSN: 10/659,734 PATENT

161. (New). The polymer of claim 160, wherein the R¹ attached to C₃ is lower alkyl.

- 162. (New). The polymer of claim 155, wherein the R^1 attached to C_4 is alkyl, and all other R^1 and R^2 variables are H.
- 163. (New). The polymer of claim 155, wherein said PEG is linear and the polymer is homobifunctional.
- 164. (New). The polymer of claim 37, wherein the PEG has a nominal average molecular mass of from about 100 daltons to about 100,000 daltons.
- 165. (New). The polymer of claim 164, wherein the PEG has a nominal average molecular mass of from about 1,000 daltons to about 50,000 daltons.
- 166. (New). The polymer of claim 165, wherein the PEG has a nominal average molecular mass of from about 2,000 daltons to about 30,000 daltons.
 - 167. (New). A hydrate or acetal form of the water-soluble polymer of claim 37.
 - 168. (New). A hydrate or acetal form of the water-soluble polymer of claim 45.
- 169. (New). The acetal of claim 167, wherein said acetal is selected from the group consisting of dimethyl acetal, diethyl acetal, di-isopropyl acetal, dibenzyl acetal, 2,2,2-trichloroethyl acetal, bis(2-nitrobenzyl) acetal, S,S'-dimethyl acetal, and S,S'-diethyl acetal.
- 170. (New). The acetal of claim 168, wherein said acetal is selected from the group consisting of dimethyl acetal, diethyl acetal, di-isopropyl acetal, dibenzyl acetal, 2,2,2-trichloroethyl acetal, bis(2-nitrobenzyl) acetal, S,S'-dimethyl acetal, and S,S'-diethyl acetal.
 - 171. (New). The water soluble polymer of claim 37, protected as a dioxolane.

172. (New). The water soluble polymer of claim 45, protected as a dioxolane.

173. (New). A conjugate formed by reaction of a biologically active agent with the polymer of claim 37.

- 174. (New). A conjugate formed by reaction of a biologically active agent with the polymer of claim 45.
- 175. (New). A conjugate formed by reaction of a biologically active agent with the polymer of claim 46.
- 176. (New). The polymer of claim 37, having a purity of at least about 95%, based upon polymeric contaminants.
- 177. (New) A pharmaceutical composition comprising a polymer conjugate of claim 175.
- 178. (New). A pharmaceutical composition comprising a polymer conjugate of claim 176.
 - 179. (New). A polymer conjugate having the following structure:

$$PEG-(CH_2)_a - C-NH - (CH_2CH_2O)_b - \begin{bmatrix} R^1 \\ I \\ C \\ R^2 \end{bmatrix}_{L} + C-NH-biologically active agent$$

where

PEG is poly(ethylene glycol),

a ranges from 0 to 6,

b ranges from 0 to 20,

z' is an integer from 1 to about 21,

PATENT

R¹, in each occurrence, is independently H or an organic radical selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkynyl, aryl, and substituted aryl;

R², in each occurrence, is independently H or an organic radical selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkynyl, aryl, and substituted aryl, and

"-NH-biologically active agent "represents a biologically active agent comprising an amino group.

180. (New) The conjugate of claim 179, wherein b is selected from the group consisting of 2, 3, 4, 5, 6, 7, 8, 9, and 10.

181. (New). The conjugate of claim 180, having the structure:

$$\begin{array}{c} O \\ O \\ II \\ C-NH-(CH_2CH_2O)_b \\ \hline \\ C_4 \\ \hline \\ C_3 \\ \hline \\ C_2 \\ \hline \\ C_2 \\ \hline \\ C_1 \\ \hline \\ C_1 \\ \hline \\ C_1 \\ \hline \\ NH-biologically active agent \\ I \\ I \\ R^2 \\ R^2 \\ R^2 \\ H \end{array}$$

182. (New). The conjugate of claim 181, wherein said PEG has a structure selected from the group consisting of linear, branched and forked.

183. (New). The conjugate of claim 182, wherein said PEG has a nominal average molecular mass selected from the group consisting of: from about 100 to about 100,000 daltons, from about 500 to about 80,000 daltons, from about 1,000 to about 50,000 daltons, and from about 2,000 to about 25,000 daltons.

184. (New). A hydrogel formed using the polymer of claim 37.

185. (New). A hydrogel formed using the polymer of claim 45.